



Published in final edited form as:

*Diabetologia*. 2013 May ; 56(5): 947–948. doi:10.1007/s00125-013-2866-4.

## Programming of DNA methylation in type 2 diabetes

**R. A. Simmons**

Perelman School of Medicine at University of Pennsylvania, Biomedical Research Building II/III  
Rm. 1308, 421 Curie Boulevard, Philadelphia, PA 19104, USA

R. A. Simmons: rsimmons@mail.med.upenn.edu

### Keywords

DNA methylation; Epigenetics; Islets; Type 2 diabetes

Type 2 diabetes mellitus is the most common metabolic disorder worldwide. It is a complex metabolic disease that is caused by insulin resistance and beta cell dysfunction. There is strong evidence that type 2 diabetes exemplifies the complex interactions between environmental and genetic determinants. During the last decade, considerable progress has been made in the identification of type 2 diabetes risk genes. This is largely a result of the development of affordable high-density single-nucleotide polymorphism (SNP) arrays that have enabled several successful genome-wide association scans to be carried out in large case-control cohorts. The first type 2 diabetes-associated variant to be identified was in the *TCF7L2* gene, which encodes a transcription factor in the Wnt signalling pathway (1). To date, it remains the variant with the largest effect size; each copy of the T allele at rs7903416 carries a 1.4–1.5 increased odds of type 2 diabetes (2, 3). Candidate gene studies identified variants in *PPARG* and *KCNJ11* (4, 5). Genome-wide association studies and the sequencing of the entire human genome have made possible the development of genotyping platforms consisting of only a few hundred thousand SNPs that could statistically capture the majority of genetic variation in the human genome. These studies have identified several more variants with smaller effect sizes. Independent replicated genetic type 2 diabetes associations now numbers 38, with most variants increasing an individual's relative odds of type 2 diabetes by a modest 5–15%.

The research on these identified loci is, however, still at an early stage, and the translation into molecular mechanisms is a big challenge as the majority are located far from any transcribed gene or near genes without any evident link to diabetes. A more extensive knowledge of transcription regulation mechanisms and the impact of differential environmental exposures is likely to provide insight into the relationship between genetics and environment. Epigenetics is starting to shed light on this complex issue, as epigenetic modifications are important regulators of transcription and are, at the same time, modifiable by the environment. Epigenetics often refers to changes in gene expression that take place without a change in the DNA sequence. The most extensively studied epigenetic changes are DNA methylation, which predominantly take place at the carbon-5 position of cytosine in a cytosine–phosphate–guanine (CpG) dinucleotide. Approximately 70% of CpG dinucleotides in human DNA are constitutively methylated, and most of the unmethylated CpGs are

---

#### Duality of interest

The author declares that there is no duality of interest associated with this manuscript.

#### Contribution statement

The author was the sole contributor to this paper.

located in CpG islands. CpG islands are CG-rich sequences located near coding sequences that serve as promoters for their associated genes. While it is well established that DNA hypermethylation at promoters and repetitive sequences is involved in stable silencing, it is largely unclear whether non-promoter DNA methylation contributes to regulation of gene expression. Furthermore, it is not yet certain whether methylation of single CpG sites in intergenic regions regulates gene expression. It is possible that these sites may represent transcription factor binding sites and serve as distal regulatory elements.

In recent years, we have begun to appreciate how genetic variants may impact epigenetic processes. A number of studies have now demonstrated that genomic variants can affect the methylation status of immediately surrounding CpGs in the region (6–9). The mechanisms responsible for changes in DNA methylation in these regions remain to be fully elucidated. A genetic variant can also introduce or remove a CpG site, which has the potential to influence DNA methylation at that site. While these changes in DNA methylation have the potential to influence gene expression as described above, it remains to be determined if this indeed the case.

In this issue of *Diabetologia*, Dayeh et al report that 19 of 40 SNPs associated with type 2 diabetes introduce or remove a CpG site. They assayed DNA methylation of these CpG-SNPs in islets of non-diabetic human donors and found that DNA methylation of all of the CpG-SNPs was significantly different from the wild-type sequences. The expression of genes located 500 kb up- or downstream of the CpG-SNP was measured using microarray analysis, and two CpG-SNPs with increased methylation were found to also have decreased mRNA expression in human islets. However, the changes in expression were quite small. This could be due to analysis by microarray rather than quantitative PCR, and it is possible that these changes could be greater. To determine whether changes in DNA methylation at CpG-SNPs were correlated with changes in islet cell function, insulin and glucagon secretion were measured in isolated islets. Islets from individuals with CpG-SNPs in *ADCY5* and *HHEX* (candidate genes regulating insulin secretion) and *CDKN2A* (candidate gene thought to influence insulin content) were found to have lower insulin content and insulin secretion, whereas glucagon secretion was higher in islets with CpG-SNPs in *ADCY5* and *KCNQ1* (genes regulating glucagon secretion). There was substantial variability in these measures, which is to be expected in human islets and it is not clear how strong the association is between the type 2 diabetes CpG-SNPs with differential DNA methylation and islet function. Nevertheless, these findings are intriguing and represent the first studies examining CpG-SNPs and DNA methylation in human islets. If these findings can be replicated in peripheral blood cells of living individuals, this may enable the identification of population subgroups at particularly high risk for type 2 diabetes and facilitate the targeting of preventative efforts to those who might benefit from them the most.

## Abbreviations

<b>CpG</b>	Cytosine–phosphate–guanine
<b>SNP</b>	Single-nucleotide polymorphism

## References

1. Reynisdottir I, Thorleifsson G, Benediktsson R, et al. Localization of a susceptibility gene for type 2 diabetes to chromosome 5q34-q35.2. *American Journal of Human Genetics*. 2003; 73:323–335. [PubMed: 12851856]
2. Grant SFA, Thorleifsson G, Reynisdottir I, et al. Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes. *Nature Genetics*. 2006; 38:320–323. [PubMed: 16415884]

3. Billings LK, Florez JC. The genetics of type 2 diabetes: What have we learned from GWAS? *Annals of the New York Academy of Sciences*. 2010; 1212:59–77. [PubMed: 21091714]
4. Altshuler D, Hirschhorn JN, Klannemark M, et al. The common PPAR $\gamma$  Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nature Genetics*. 2000; 26:76–80. [PubMed: 10973253]
5. Gloyn AL, Weedon MN, Owen KR, et al. Large-scale association studies of variants in genes encoding the pancreatic  $\beta$ -cell K<sub>ATP</sub> channel subunits Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) confirm that the *KCNJ11* E23K variant is associated with type 2 diabetes. *Diabetes*. 2003; 52:568–572. [PubMed: 12540637]
6. Shoemaker R, Deng J, Wang W, Zhang K. Allele-specific methylation is prevalent and is contributed by CpG-SNPs in the human genome. *Genome Res*. 2010; 20:883–889. [PubMed: 20418490]
7. Taqi MM, Bazov I, Watanabe H, et al. Prodynorphin CpG-SNPs associated with alcohol dependence: elevated methylation in the brain of human alcoholics. *Addiction Biology*. 2011; 16:499–509. [PubMed: 21521424]
8. Harlid S, Ivarsson MI, Butt S, et al. A candidate CpG SNP approach identifies a breast cancer associated ESR1-SNP. *Int J Cancer*. 2011; 129:1689–1698. [PubMed: 21105050]
9. Tsai PC, Spector TD, Bell JT. Using epigenome-wide association scans of DNA methylation in age-related complex human traits. *Epigenomics*. 2012; 4:511–526. [PubMed: 23130833]
10. Dayeh TA, Olsson AH, Volkow P, Almgren P, Rönn T, Ling C. Identification of CpG-SNPs associated with type 2 diabetes and differential DNA methylation in human pancreatic islets. *Diabetologia*. 201310.1007/s00125-012-2815-7